AMENDMENTS TO THE CLAIMS

In the claims:

1. (Currently amended) A transgenic mouse whose genome comprises homozygous non-functional ~~comprising at least one nonfunctional allele of a~~ beta-secretase-1 (BACE-1) ~~gene~~ genes, wherein the genes comprise a ~~allele is rendered nonfunctional by~~ deletion ~~of~~ in exons 4-8 of the BACE-1 gene and the mouse lacks functional BACE-1.

2. (Canceled)

3. (Canceled)

4. (Canceled)

5. (Currently amended) The transgenic mouse of claim 1, wherein the mouse or an ancestor thereof was produced by homologous recombination between an endogenous ~~allele of the~~ BACE-1 gene and a construct containing a positive selection marker flanked by segments showing sufficient sequence relatedness to the BACE-1 gene for the construct to recombine with the endogenous ~~allele~~ gene introducing the positive selection marker into the ~~endogenous allele~~ BACE-1 gene and rendering ~~it~~ the gene nonfunctional.

6. (Currently amended) The transgenic mouse of claim 1, wherein the mouse or an ancestor thereof was produced by homologous recombination between an endogenous ~~allele of the~~ BACE-1 gene and a construct containing a positive selection marker flanked by segments showing sufficient sequence relatedness to the BACE-1 gene to undergo homologous recombination with it, these segments being flanked by frt recombination sites, whereby the construct recombines with the endogenous gene introducing the positive selection marker and frt recombination sites into the endogenous ~~allele~~ gene, and the frt recombination sites undergo recombination with each other thereby excising DNA between the flp recombination sites resulting in a deleted nonfunctional ~~form of the endogenous allele~~ BACE -1 gene.

7. -8. (Canceled)

9. (Currently amended) The transgenic mouse of claim 1, wherein the ~~allele~~ gene is rendered nonfunctional by homologous recombination with a targeting vector comprising a lambda KOS genomic clone of BACE-1.

10.-12 (Canceled)

13. (Currently amended) The transgenic mouse of claim 1, whose genome further ~~comprising~~ comprises a transgene comprising a DNA sequence encoding an ~~mutation in the~~ APP ~~gene associated with~~ having a familial Alzheimer's disease mutation.

14. (Previously presented) The transgenic mouse of claim 13, wherein the transgene comprises a mutation at codons 595 and 596 of human APP695, or an isoform or fragment thereof, wherein the amino acid residues at positions corresponding to positions 595 and 596 are asparagine and leucine, respectively.

15. (Previously presented) The transgenic mouse of claim 13, wherein the transgene comprises a mutation at codon 717 of APP770 or an isoform or fragment of APP770 having a mutant amino acid residue at position 717.

16. (Previously presented) The transgenic mouse of claim 13, wherein the mutant amino acid residue is isoleucine, phenylalanine or glycine.

17. (Currently amended) The transgenic mouse of ~~claims~~ claim 13, wherein the mouse is homozygous for the non-functional ~~allele~~ BACE-1 gene.

18. (Previously presented) The transgenic mouse of claim 13, wherein the mouse is heterozygous for the transgene.

19. (Currently amended) A cortical cell culture derived from the transgenic mouse of claim 1, wherein the cells lack functional BACE-1.

20. (Previously presented) The cortical cell culture of claim 19, wherein the cell culture is a primary cell culture.

21. (Previously presented) The cortical cell culture of claim 19, wherein the cell culture comprises a detectable amount of a peptide recognized by an antibody that recognizes residues 13-28 of Aβ.

22. (Currently amended) A method for screening for an inhibitor of the production of an Aβ peptide by a protease other than BACE-1, wherein the ~~of a~~ peptide is recognized by an antibody that recognizes residues 13-28 of Aβ comprising

exposing a transgenic mouse whose genome comprises homozygous non-functional BACE-1 genes, ~~lacking a functional allele of a beta-secretase-1 (BACE-1) gene~~ wherein the mouse lacks functional BACE-1, or a cortical cell culture derived ~~therefrom~~ from the mouse, wherein the cells lack functional BACE-1 to an agent, and

detecting the ~~peptide produced in the transgenic mouse or cell culture exposed to the agent~~ production of an Aβ with an antibody that recognizes residues 12-28 of Aβ,

wherein a reduced amount of Aβ peptide produced in the exposed transgenic mouse or cortical cell culture relative to ~~a~~ the transgenic mouse or the cortical cell culture ~~which has~~ not ~~been~~ exposed to the agent is indicative of inhibitory activity.

23. (Previously presented) The method of claim 22, wherein a cortical cell culture is exposed to the agent.

24. (Previously presented) The method of claim 22, wherein the cortical cell culture is a primary cell culture.

25. (Currently amended) A method of analyzing potential side-effects for an inhibitor of beta-secretase, comprising:

exposing a transgenic mouse whose genome ~~comprising~~ comprises ~~at least one~~ homozygous nonfunctional ~~allele of a beta-secretase 1 (BACE-1) gene~~ BACE-1 genes, wherein the mouse lacks functional BACE-1, or a cortical cell culture derived from the mouse, ~~therefrom~~ where the cells lack functional BACE-1 to an inhibitor of ~~beta-secretase~~ BACE-1; and

measuring whether there is a change in the level of at least one component of the transgenic mouse or cortical cell in response ~~responsive~~ to the administration of the inhibitor relative to the transgenic mouse or the cell culture not exposed to the agent; wherein a change in the level of at least one component indicates a potential side effect of the inhibitor.

26. (Previously presented) The method of claim 25, wherein the measuring step measures changes in the levels of a plurality of mRNA species.

27. (Currently amended) A mouse embryonic stem cell ~~comprising at least one~~ whose genome comprises a nonfunctional ~~allele of a beta-secretase 1 (BACE-1)~~ gene for BACE-1 genes, wherein the ~~allele is rendered nonfunctional by~~ gene comprises a deletion ~~of~~ in exons 4-8 of the BACE-1 gene.

28. (Currently amended) The mouse embryonic stem cell of claim 27, wherein the cell ~~that~~ is homozygous for the ~~allele~~ deletion of the BACE-1 gene.

29. (Cancel)

30. (Previously presented) The mouse embryonic stem cell of claim 27 produced by homologous recombination with a targeting vector designed in a way that, upon homologous recombination, exons 4 to 8 of the BACE-1 gene are flanked with FLP recombinase target sites (frt sites).

31. (Previously presented) The mouse embryonic stem cell of claim 30, produced by homologous recombination with a targeting vector designed in a way that, with respect to the genomic locus, the 5' region of homology covered 4.5 kb and the 3' region 4.3 kb until the third frt site, and an additional 1.5 kb further 3'.

32. (Currently amended) The mouse embryonic stem cell of claim 27 that is homozygous for a nonfunctional ~~allele~~ BACE-1 gene lacking exons 4-8 ~~of BACE-1~~.

33. (Previously presented) The mouse embryonic stem cell of claim 27, produced by homologous recombination with a first targeting vector that introduces a neomycin resistance gene in the BACE-1 gene and with a second targeting vector that replaces the neomycin resistance gene with a hygromycin resistance gene cassette.

34. (Currently amended) A blastocyst ~~formed~~ produced by ~~differentiation~~ insertion of ~~a~~ the mouse embryonic stem cell ~~as described in~~ of claim 27.

35. (Currently amended) A method for generating a transgenic mouse comprising at least one nonfunctional ~~allele of a beta-secreatse-1 (BACE-1)~~ BACE-1 gene, the method comprising:

introducing at least one genetic construct into a mouse embryonic stem cell ~~line~~, the genetic construct comprising a positive selection marker flanked by segments showing sufficient sequence relatedness to the BACE-1 gene to undergo homologous recombination with it, these segments being flanked by frt recombination sites;

screening for cells in which recombination has occurred between the genetic construct and the endogenous gene;

injecting the mouse embryonic stem cells, which have undergone recombination, into blastocysts to generate chimeric ~~mice~~ blastocysts;

developing the chimeric blastocysts into chimeric mice;

breeding the chimeric mice with mice of the type which provided the blastocysts to generate ~~the chimeric~~ mice ~~to generate mice~~ heterozygous for the nonfunctional ~~allele~~ gene of BACE-1; and

breeding the mice heterozygous for the nonfunctional ~~allele of~~ BACE-1 gene with mice transgenic for flp recombinase resulting in transgenic mice whose genome comprises a nonfunctional ~~form of the endogenous~~ BACE-1 ~~allele~~ gene.

36. (Currently amended) The method of claim 35, wherein the ~~allele~~ gene is rendered nonfunctional by deletion of at least a segment ~~from~~ of exon 1.

37. (Currently amended) The method of claim 35, wherein the ~~allele~~ gene is rendered nonfunctional by deletion of exons 4-8.

38. (Currently amended) A transgenic mouse comprising at least one nonfunctional ~~allele of a beta-secretase 1 (BACE 1)~~ BACE-1 gene, wherein the mouse or an ancestor thereof was produced by homologous recombination between an endogenous ~~allele of the~~ BACE-1 gene and a construct containing a positive selection marker flanked by segments showing sufficient sequence relatedness to the gene to undergo homologous recombination with it, these segments being flanked by frt recombination sites, whereby the construct recombines with the endogenous gene introducing the positive selection marker and frt recombination sites into the endogenous ~~allele~~ gene, and the frt recombination sites undergo recombination with each other thereby excising DNA between the flp recombination sites resulting in a ~~deleted~~ nonfunctional ~~form of the~~ endogenous ~~allele~~ BACE-1 gene.

39. (Currently amended) The transgenic mouse of claim 38, wherein the mouse ~~that~~ is homozygous for the ~~allele~~ nonfunctional endogenous BACE-1 gene.

40. (Canceled)

41. (Canceled)

42. (Currently amended) The transgenic mouse of claim 38, wherein the ~~allele~~ gene is rendered nonfunctional by deletion of at least a segment ~~of~~ from an exon of the gene.

43. (Currently amended) The transgenic mouse of claim 38, wherein the ~~allele~~ gene is rendered nonfunctional by deletion of at least a segment from exon 1.

44. (Currently amended) The transgenic mouse of claim 38, wherein the ~~allele~~ gene is rendered nonfunctional by a 165 base pair deletion of exon 1 starting from 2 base pairs past the initiating methionine and extending through the end of exon 1 replaced with an expression cassette in the targeting vector electroporated into 129 ES cells to generate the transgenic mouse.

45. (Currently amended) The transgenic mouse of claim 38, wherein the ~~allele~~ gene is rendered nonfunctional by deletion of exons 4-8.

46. (Currently amended) The transgenic mouse of claim 38, whose genome further ~~comprising~~ comprises a transgene comprising a ~~mutation in the~~ DNA sequence encoding an APP ~~gene associated with~~ having familial Alzheimer's disease mutation.

47. (Previously presented) The transgenic mouse of claim 46, wherein the transgene comprises a mutation at codons 595 and 596 of human APP695, or an isoform or fragment thereof, wherein the amino acid residues at positions corresponding to positions 595 and 596 are asparagine and leucine, respectively.

48. (Previously presented) The transgenic mouse of claim 46, wherein the transgene comprises a mutation at codon 717 of APP770 or an isoform or fragment of APP770 having a mutant amino acid residue at position 717.

49. (Previously presented) The transgenic mouse of claim 46, wherein the mutant amino acid residue is isoleucine, phenylalanine or glycine.

50. (Currently amended) A cortical cell culture derived from the transgenic mouse of claim 38, wherein the cells lack functional BACE-1.

51. (Previously presented) The cortical cell culture of claim 38, wherein the cell culture is a primary cell culture.

52. (Previously presented) The cortical cell culture of claim 38, wherein the cell culture comprises a detectable amount of a peptide recognized by an antibody that recognizes residues 13-28 of Aβ.

53. (Previously presented) The cortical cell culture of claim 21, wherein the peptide recognized by an antibody that recognizes residues 13-28 of Aβ is β-amyloid.

54. (Previously presented) The method of claim 22, wherein the peptide recognized by an antibody that recognizes residues 13-28 of Aβ is β-amyloid.

55. (Previously presented) The cortical cell culture of claim 52, wherein the peptide recognized by an antibody that recognizes residues 13-28 of Aβ is β-amyloid.